BIOGRAPHICAL SKETCH

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NAME: Michail S. Lionakis

eRA COMMONS USER NAME (credential, e.g., agency login): lionakism

POSITION TITLE: Senior Investigator; Chief, Fungal Pathogenesis Section

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Crete, Greece	M.D., Sc.D.	07/2000	Medicine
University of Texas MD Anderson Cancer Center	Postdoctoral	05/2004	Mycology
Baylor College of Medicine		06/2007	Internal Medicine Residency
National Institute of Allergy and Infectious Diseases		06/2009	Infectious Diseases Clinical Fellowship
National Institute of Allergy and Infectious Diseases, Laboratory of Molecular Immunology	Postdoctoral	06/2012	Immunology

A. Personal Statement

I am a physician-scientist and Head of the Fungal Pathogenesis Section in the Laboratory of Clinical Immunology and Microbiology, NIAID. My laboratory research focuses on 1) better understanding the genetic and immune defects that underlie enhanced susceptibility to mucocutaneous and invasive fungal infections in humans and on 2) cellular and molecular factors that regulate the immune response against mucosal and invasive candidiasis and invasive aspergillosis in clinically relevant animal models. My long-term goals are 1) to understand the pathogenesis of mucosal and invasive candidiasis and invasive aspergillosis, 2) to use this knowledge to identify patients at risk for developing these diseases and to improve their outcomes, 3) to improve care for patients with inherited susceptibility to fungal disease such as Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED), Caspase recruitment domain-containing protein 9 (CARD9) deficiency and others, and 4) to discover novel genetic predisposing factors for human fungal disease. To this end, we utilize *in vitro* cell culture systems and clinically relevant mouse models of mucosal and systemic *Candida* infections and pulmonary *Aspergillus* infections, and we enroll patients with inherited and acquired susceptibility to candidiasis and aspergillosis to study host-fungal interactions by using a variety of immunological, biological, and imaging approaches.

1. Drummond RA, Collar AL, Swamydas M, Rodriguez C, Lim JK, Mendez LM, Fink DL, Hsu AP, Zhai B, Karauzum H, Mikelis CM, Rose SR, Ferre EMN, Yocke L, Lemberg K, Kuehn HS, Rosenzweig SD, Lin X, Chittiboina P, Datta SK, Belhorn TH, Weimer ET, Hernandez ML, Hohl TM, Kuhns DB, and Lionakis MS*. CARD9-dependent neutrophil recruitment protects against fungal invasion of the central nervous system. 2015; *PLoS Pathog.* 11(12): e1005293.
2. Swamydas M, Gao JL, Break TJ, Johnson MD, Jaeger M, Green NM, Fischer B, Rodriguez C, Lim JK, Perfect J, Alexander B, Kullberg BJ, Netea MG, Murphy PM and Lionakis MS*. CXCR1-mediated neutrophil degranulation and fungal killing promotes *Candida* clearance and host survival. 2016; *Sci Transl Med.* 8(322): 322ra10.
3. Lionakis MS, Dunleavy K, Roschewski M, Widemann BC, Butman JA, Schmitz R, Cole DE, Melani C, Higham CS, Desai JV, Ceribelli M, Chen L, Thomas CJ, Little RF, Gea-Banacloche J, Bhaumik S, Stetler-Stevenson M, Pittaluga S, Jaffe ES, Heiss J, Lucas N, Steinberg SM, Staudt LM and Wilson WH. Inhibition of B cell receptor signaling by ibrutinib in primary central nervous system

lymphoma. *Cancer Cell*. 2017; 31(6):833-843.e5

4. Rieber N, Gazendam RP, Freeman AF, Hsu AP, Collar AL, Drummond RA, Sugui JA, Rongkavilit C, Hoffman K, Henderson C, Clark L, Mezger M, Swamydas M, Engehohm M, Schule R, Neumayer B, Ebel F, Mikelis CM, Pittaluga S, Prasad VK, Singh A, Milner JD, Williams KW, Lim JK, Kwon-Chung KJ, Holland SM, Hartl D, Kuijpers TW, and Lionakis MS*. Extrapulmonary *Aspergillus* infection in patients with CARD9 deficiency. *JCI Insight*. 2016; 1(17): e89890.

* Corresponding author

B. Positions and Honors

Positions and Employment

2000-2002 Rural physician, Greek Ministry of Health & Welfare, Katerini, Greece
2002-2004 Post-doctoral research fellow, Department of Infectious Diseases, The University of Texas MD Anderson Cancer Center, Houston, TX
2004-2007 Internal Medicine Resident, Baylor College of Medicine, Houston, TX
2007-2010 Infectious Diseases Fellow, NIAID, NIH, Bethesda, MD
2010-2012 Assistant Clinical Investigator, Chief, Clinical Mycology Unit, Laboratory of Molecular Immunology, NIAID, NIH, Bethesda, MD
2012-2017 Tenure-Track Investigator, Chief, Fungal Pathogenesis Unit, Laboratory of Clinical Infectious Diseases, NIAID, NIH, Bethesda, MD
2017-Present Senior (Tenured) Investigator, Chief, Fungal Pathogenesis Section, Laboratory of Clinical Immunology and Microbiology, NIAID, NIH, Bethesda, MD

Licensures and Board Certifications

2007-Present Board-certified in Internal Medicine
2009-Present Board-certified in Infectious Diseases
2007-Present Licensed in the State of Maryland

Other Experience and Professional Memberships

2004-present Associate, American College of Physicians (ACP)
2005-present Member, American Society of Microbiology (ASM)
2007-present Member, Infectious Diseases Society of America (IDSA)
2010-present Member, International Immunocompromised Host Society (ICHS)
2010-present Member, Mycoses Study Group (MSG)
2010-present Attending physician, Infectious Diseases Consult Service, NIAID, NIH, Bethesda, MD
2012-present Member, International Society for Human and Animal Mycology (ISHAM)
2012-present Chair, NIH Clinicopathologic Grand Rounds Committee
2012-present Editorial Advisory Board Member, The Journal of Infectious Diseases
2012-present Editorial Board Member, Virulence
2014-2017 Member, IDWeek Program Committee
2014-present Group Leader, Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Mucocutaneous Candidiasis (http://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment- guidelines/331/candida)
2015-present Member, Clinical Immunology Society (CIS)
2015-present Member, American Association of Immunologists (AAI)
2015-2017 Member, NIH Immunology Interest Group (IIG) Steering Committee
2015-present Associate Editor, Frontiers in Cellular and Infection Microbiology
2016-present Editorial Board Member, Infection and Immunity
2016-present Board of Consulting Editors, JCI Insight
2016-present Member, Medical Advisory Committee, APS-1 Foundation

Honors

2000 GlaxoWellcome Pharmaceutical Company scholarship award
2003 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) Program Committee Award from ASM for Outstanding Research in the Pathogenesis of Microbial Diseases

2003 Research Patent "Biopanning as an approach to study the pathogenesis of and produce novel treatment modalities for invasive aspergillosis", Patent Serial No: 60/502,509
2004 1st place winner of the Bristol-Myers Squibb Award in Clinical/Translational Research
2005 Offered position of Chief Medical Resident, Department of Internal Medicine, Baylor College of Medicine
2007 Henry D. McIntosh Award for Outstanding Resident in Medicine, Baylor College of Medicine
2009 49th ICAAC Infectious Disease Fellows Grant Program Award from ASM
2010 50th ICAAC George McCracken Infectious Disease Fellow Award from ASM
2013 Performance Award, National Institute of Allergy & Infectious Diseases, NIH
2014 Performance Award, National Institute of Allergy & Infectious Diseases, NIH
2015 Performance Award, National Institute of Allergy & Infectious Diseases, NIH
2015 Awarded the "Ultimate Prize" of the Rare Genomic Institute's "BeHEARD Science Challenge"
2015 IDWeek Investigator Award
2016 Fellow, IDSA
2016 Performance Award, National Institute of Allergy & Infectious Diseases, NIH
2017 Performance Award, National Institute of Allergy & Infectious Diseases, NIH
2017 ACP Walter J. McDonald Award for Early Career Physicians
2018 Junior Investigator Award, Immunocompromised Host Society (ICHS)

C. Contribution to Science

1. Systemic candidiasis is a leading cause of nosocomial bloodstream infection in the US and is associated with mortality that exceeds 40% despite therapy. We conducted the first study to define comprehensively the accumulation of leukocyte subsets in blood and 4 major organs of mice infected systemically with *Candida* (*J Innate Immun*, 2011). This study was the first to clearly show that the innate immune system responds in an organ-specific temporal and spatial manner, and varies markedly in its ability to control *Candida* growth and filamentation, a key virulence factor. These findings highlight the need for further research on organ-specific cellular and molecular factors that modulate the immune response to *Candida* and other pathogens that exhibit tissue-specific tropisms.

   a) Lionakis MS, Lim JK, Richard Lee CC and Murphy PM. Organ-specific innate immune responses in a mouse model of invasive candidiasis. *J Innate Immun*. 2011; 3(2): 180-99.

2. Our research has subsequently discovered critical mediators of immune cell localization, recruitment and effector function during systemic candidiasis. Combining innovative basic research approaches and clinical research, our group is systematically dissecting the web of chemokine receptor function and trafficking of innate immune cells during systemic candidiasis. So far, we have identified the function of three chemokine receptors, CCR1, CX3CR1, and CXCR1, in host defense to *Candida* in mice and humans. Using a broad screen that measured mRNA expression of chemokines and their receptors in response to *Candida* infection, we discovered that CCR1 is responsible for fatal neutrophil-driven renal immunopathology (*PLoS Pathogens*, 2012; *Antimicrob Agents Chemother*, 2017). This study was the first to uncover a chemotactic factor that mediates neutrophil recruitment specifically into the kidneys in any infectious disease. Concurrent with this work, we built on the knowledge that CX3CR1 is a long recognized marker of macrophages, which are important for *Candida* pathogenesis. We then showed that CX3CR1-mediated macrophage survival promotes *Candida* control in a mouse model. As published in the *Journal of Clinical Investigation* (2013), we also identified a genetic allele (*CX3CR1-M280*) in humans that is associated with systemic candidiasis. Monocytes isolated from patients carrying this allele exhibit impaired survival and the patients are monocytopenic (*JCI Insight*, 2018), further implicating CX3CR1 in human disease. Most recently, we have discovered the first known functional role for the chemokine receptor CXCR1. Detailed in a manuscript published in *Science Translational Medicine* (2016), our group found that Cxcr1-dependent neutrophil degranulation and fungal killing promotes *Candida* control. Importantly, we also found that the human *CXCR1-T276* allele results in impaired degranulation and fungal killing of human neutrophils and is a risk factor for disseminated candidiasis in patients. These discoveries have provided the foundation for the design of a multicenter clinical trial to test the efficacy of

fluconazole prophylaxis in preventing candidemia and disseminated candidiasis in intensive care unit patients carrying these mutant alleles.

a) Lionakis MS*, Fischer BG, Lim J, Swamydas M, Wan W, Richard Lee C, Cohen J, Scheinberg P, Gao JL and Murphy PM. Chemokine receptor Ccr1 drives neutrophil-mediated kidney immunopathology and mortality in invasive candidiasis. *PLoS Pathog*. 2012; 8(8): e1002865.
b) Lionakis MS*, Swamydas M, Fischer B, Plantinga TS, Johnson MD, Jaeger M, Green NM, Masenduskas A, Weigert R, Mikelis C, Wan W, Richard Lee CC, Lim JK, Rivollier A, Yang JC, Laird GM, Wheeler RT, Alexander BD, Perfect JR, Gao J, Kullberg BJ, Netea MG and Murphy PM. CX3CR1-dependent renal macrophage survival promotes *Candida* control and host survival. *J Clin Invest.* 2013; 123(12): 5035–5051.
c) Swamydas M, Gao JL, Break TJ, Johnson MD, Jaeger M, Green NM, Fischer B, Rodriguez C, Lim JK, Perfect J, Alexander B, Kullberg BJ, Netea MG, Murphy PM and Lionakis MS*. CXCR1-mediated neutrophil degranulation and fungal killing promotes *Candida* clearance and host survival. 2016; *Sci Transl Med.* 8(322): 322ra10.
d) Collar AL, Swamydas M, O'Hayre M, Sajib MS, Hoffman KW, Singh SP, Mourad A, Johnson MD, Ferre EMN, Farber JM, Lim JK, Mikelis CM, Gutkind JS, Lionakis MS*. The homozygous *CX3CR1-M280* mutation impairs human monocyte survival. *JCI Insight*. 2018; 3(3): 95417.
* Corresponding author

3. Parallel to these studies, we established the largest prospectively-evaluated cohort of patients in the world (~100) with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), an autosomal recessive monogenic disorder that manifests with multiorgan autoimmunity and chronic mucocutaneous candidiasis making NIH a major referral center for this primary immunodeficiency. Via direct clinical care, clinical research and bench research in *Aire*$^{-/-}$ mice, we have been developing research on the mechanisms by which Aire deficiency promotes mucosal fungal susceptibility (Break et al, submitted) and multiorgan autoimmunity (Ferre et al., submitted) with the ultimate goal of devising improved diagnostic, preventive and therapeutic interventions. We have thus far redefined the clinical features and diagnostic criteria of APECED, which should result in earlier recognition, prompt initiation of immunomodulation and improved patient outcomes (*JCI Insight*, 2016). We have also collaborated with Dr. Mathis and have extended her novel mouse data on the Aire-dependent role of γδ T cells in induction of organ-specific autoimmunity to our patient cohort (*Immunity*, 2016).

a) Ferre EMN, Rose SR, Rosenzweig SD, Burbelo P, Romito KR, Niemela JE, Rosen LB, Break TJ, Gu W, Hunsberger S, Browne SK, Hsu AP, Rampertaap S, Swamydas M, Collar AL, Kong HH, Lee CR, Chascsa D, Simcox T, Pham A, Bondici A, Natarajan M, Monsale J, Kleiner D, Quezado M, Alevizos I, Moutsopoulos N, Yockey L, Frein C, Soldatos A, Calvo K, Adjemian J, Similuk MN, Lang DM, Stone KD, Uzel G, Kopp JB, Bishop RJ, Holland SM, Olivier KN, Fleisher TA, Heller T, Winer KK, and Lionakis MS*. Redefined clinical features and diagnostic criteria in Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *JCI Insight*. 2016; 1(13): e88782.
b) Fujikado N, Mann A, Bansal K, Romito KR, Ferre EMN, Rosenzweig SD, Lionakis MS, Benoist C, Mathis DM. Aire inhibits the generation of a perinatal population of interleukin-17A-producing γδ T cells to promote immunologic tolerance. *Immunity*. 2016; 45(5): 999-1012.
* Corresponding author

4. We have also built the largest single-center cohort of patients with CARD9 deficiency (~20 patients), an autosomal recessive monogenic disorder that results in spontaneous fungal infections that have a tropism for the central nervous system (CNS), making NIH a major referral center for this primary immunodeficiency. By uniting direct clinical care, clinical research and bench investigations, our work has resulted in the identification of novel *CARD9* mutations, the delineation of the function of CARD9 in promoting tissue-specific and fungal-specific neutrophil recruitment and control of fungal invasion in the CNS (*PLoS Pathogens*, 2015), and the discovery of an intricate Candidalysin/IL-1β/CXCL1 network of microglia-mediated neutrophil recruitment in the fungal-infected CNS (Drummond et al., submitted). Beyond candidiasis, we have identified CARD9 deficiency as the first known inherited or acquired risk factor that predisposes to aspergillosis with a unique tropism for extrapulmonary tissues

while sparing the lung, which is the typical portal of entry of *Aspergillus* and the organ involved uniformly in *Aspergillus*-infected patients without CARD9 deficiency (*JCI Insight*, 2016).

a) Drummond RA, Collar AL, Swamydas M, Rodriguez C, Lim JK, Mendez LM, Fink DL, Hsu AP, Zhai B, Karauzum H, Mikelis CM, Rose SR, Ferre EMN, Yocke L, Lemberg K, Kuehn HS, Rosenzweig SD, Lin X, Chittiboina P, Datta SK, Belhorn TH, Weimer ET, Hernandez ML, Hohl TM, Kuhns DB, and Lionakis MS*. CARD9-dependent neutrophil recruitment protects against fungal invasion of the central nervous system. 2015; *PLoS Pathog.*11(12): e1005293.
b) Rieber N, Gazendam RP, Freeman AF, Hsu AP, Collar AL, Drummond RA, Sugui JA, Rongkavilit C, Hoffman K, Henderson C, Clark L, Mezger M, Swamydas M, Engehohm M, Schule R, Neumayer B, Ebel F, Mikelis CM, Pittaluga S, Prasad VK, Singh A, Milner JD, Williams KW, Lim JK, Kwon-Chung KJ, Holland SM, Hartl D, Kuijpers TW, Lionakis MS*. Extrapulmonary *Aspergillus* infection in patients with CARD9 deficiency. *JCI Insight.* 2016; 1(17): e89890.

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5. We have uncovered a previously unanticipated role of the Bruton tyrosine kinase (BTK), a kinase critical for B cell development and function, in immune surveillance against aspergillosis, an infection that requires myeloid cell recruitment and effector function for eradication. In an ibrutinib-based clinical trial performed at NIH in patients with central nervous system lymphoma, where patients had a remarkable response to the underlying malignancy, a high incidence of aspergillosis was noted, including infections with CNS spread. We corroborated the human findings in Btk-deficient mice that exhibited increased mortality, fungal tissue burden and lung injury after *Aspergillus* infection compared to wild-type animals (*Cancer Cell*, 2017); the cellular and molecular basis of this susceptibility are under further investigation using mouse and human systems.

a) Lionakis MS, Dunleavy K, Roschewski M, Widemann BC, Butman JA, Schmitz R, Cole DE, Melani C, Higham CS, Desai JV, Ceribelli M, Chen L, Thomas CJ, Little RF, Gea-Banacloche J, Bhaumik S, Stetler-Stevenson M, Pittaluga S, Jaffe ES, Heiss J, Lucas N, Steinberg SM, Staudt LM and Wilson WH. Inhibition of B cell receptor signaling by ibrutinib in primary central nervous system lymphoma. *Cancer Cell*. 2017; 31(6):833-843.e5.
b) Chamilos G, Lionakis MS and Kontoyiannis DP. Call for action: invasive fungal infections associated with ibrutinib and other small molecule kinase inhibitors targeting immune signaling pathway *Clin Infect Dis*. 2018; 66(1): 140-148.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/pubmed/?term=lionakis+m+OR+lionakis+MS

D. Research Support

Ongoing Research Support and Projects

As a member of the National Institute of Allergy and Infectious Diseases (NIAID) Intramural Research Program (IRP), my research is funded via the IRP. Major ongoing research projects include:

1. The role of the chemokine system in host defense against fungal infections.
   The major goals of this project are to study the role of chemokines and their receptors in mediating effective host defense against *Candida*, and to identify novel genetic markers of poor prognosis and early diagnosis for human fungal disease.
2. Organ-specific immune responses against fungal pathogens.
   The major goal of this project is to investigate the molecular and cellular factors that explain the organ-specific ability of different tissues to control the growth of fungal pathogens.
3. Natural history, immunologic and genetic defects of human mucosal and invasive fungal infections.
   The goal of this protocol is to recruit patients with mucocutaneous and invasive fungal infections at NIH to investigate the immunological mechanism(s) by which inherited and acquired immune deficiencies increase susceptibility to mucocutaneous and invasive fungal infections.
4. Multi-omics profiling of antibiotic-induced vaginal candidiasis.
   The goal of this project is to define the microbiomic and immunologic alterations that account for development of vaginal candidiasis in healthy women who receive antibiotic treatment.